melanomas exact a disproportionate toll. The data from these analyses provide strong grounds for enacting policies of melanoma education, primary prevention and close surveillance for all patients undergoing organ transplantation. Suspicious pigmented lesions should be managed promptly in all such patients. For OTRs diagnosed with melanoma, referral to expert centers would seem prudent.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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CYR61/CCN1: A Novel Mediator of Epidermal Hyperplasia and Inflammation in Psoriasis?

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The complex pathogenesis of psoriasis is still not fully understood. The study by Sun *et al.* (2015) suggests that CYR61 (now named CCN1), a secreted matricellular protein, has a role in the pathogenesis of psoriasis, and thus targeting CCN1 represents a potential therapeutic strategy in its treatment.

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CCN1 in psoriasis: new findings and clinical implications

Psoriasis is a chronic inflammatory skin disease characterized by hyperproliferation of epidermal keratinocytes and resulting in scaly, red, and well-demarcated skin lesions. Hyperproliferation is driven by the additive and synergistic activities of a plethora of cytokines and growth factors (Baliwag *et al.*, 2015) acting on and driving changes in the architecture of the epidermis, keratinocytes, resident and infiltrating immune cells, as well as fibroblasts and vascular endothelium in the dermis (Elder *et al.*, 2010). In this issue, Sun *et al.*, (2015) add another ingredient to the inflammatory recipe responsible for driving this disease; they report that the expression of CCN1, a multifunctional non-structural protein

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Clinical Implications

- CCN1 is a potential new ingredient in the recipe of inflammatory mediators that drive psoriasis.
- Targeting the interaction of CCN1 with integrin α6β1 represents a potential new strategy to treat psoriasis.
- CCN1 may function as an important regulator in skin biology, by modulating key functions of keratinocytes and fibroblasts.

found in the extracellular matrix (ECM), is elevated in the skin of patients with psoriasis, as well as in psoriasis-like mouse models. Importantly, blocking CCN1 function by either lentiviral-based sh-RNA knockdown of CCN1 or anti-CCN1 neutralizing antibodies attenuated the epidermal hyperplasia and inflammation seen in the psoriasis-like mouse models. Thus, they concluded that CCN1 participates in the pathogenesis of psoriasis and that targeting CCN1 could be an important therapeutic strategy. Although the mechanisms by which CCN1 promotes epidermal hyperplasia and inflammation are not fully understood, Sun *et al.,* (2015) present findings that CCN1 acts through integrin α6β1 on keratinocytes. This interaction activates downstream PI3K/Akt/NF-κB signaling pathways. This finding has clinical implication by suggesting α6β1 integrin as a relevant target.

CCN1 is a secreted protein that interacts with the ECM, making it a member of a large family of matricellular proteins. On the basis of structural homology, CCN proteins comprise a family of six members, CCN1-6 (Perbal, 2004). The CCN acronym is taken from the names of the first three members of the family to be discovered: CYR61/CCN1 (cysteine-rich protein 61), CTGF/CCN2 (connective tissue growth factor), and NOV/CCN3 (nephroblastoma overexpressed gene). Members of the CCN family exhibit diverse cellular functions, such as regulation of cell proliferation, chemotaxis, apoptosis, adhesion, motility, ion transport, and ECM regulation (Chen and Lau, 2009).

CCN1 has been reported to regulate cell adhesion, migration, chemotaxis, inflammation, cell–matrix interactions, synthesis of ECM proteins, and wound healing in a variety of cells in culture (Jun and Lau, 2010; Lau, 2011). CCN1 exerts this range of functions through interaction with multiple integrins in a cell-type and context-dependent manner (Figure 1) (Lau, 2011). During embryonic development, CCN1 has a critical role in vascular development and blood vessel formation in the placenta. CCN1 knockout in mice is embryonic lethal primarily due to a failure in vascular development caused by impaired ECM homeostasis. Studies in animal models and in patients have confirmed that deregulation of CCN1 protein is found in several diseases associated with chronic inflammation and/or tissue injury, including rheumatoid arthritis, atherosclerosis, diabetes-related nephropathy and retinopathy, and many forms of cancer (Chen and Lau, 2009; Kular *et al.*, 2011).

What drives sustained elevation of CCN1 in psoriatic skin?

The study by Sun *et al.* (2015) reveals elevated CCN1 in the skin of patients with psoriasis and its potential role as a driving force for epidermal hyperplasia and inflammation. Obviously, their findings raise the question of what drives the sustained elevation of CCN. Several recent studies have shown that the CCN1 expression is regulated directly by the transcriptional co-activator Yes-associated protein (YAP), a major downstream effector of the hippo signaling pathway. In mouse skin, YAP has a critical role in regulating keratinocyte proliferation, differentiation, and survival through upregulation of CCN1 (Zhang *et al.*, 2011). In the human skin cancer, basal cell carcinoma, YAP, and its downstream transcriptional target CCN1 are elevated markedly in tumor islands. In human keratinocytes, knockdown of YAP significantly reduces the expression of CCN1 and represses proliferation and survival. This inhibition of proliferation and survival is rescued by restoration of CCN1 expression (Quan *et al.*, 2014). These data provide evidence that up-regulation of YAP promotes aberrant keratinocyte proliferation through up-regulation of CCN1 in basal cell carcinoma. Although the expression of YAP in psoriasis is unknown, these data suggest that YAP may be involved in upregulating CCN1 in psoriasis.

> The study by Sun *et al.* (2015) suggests that CCN1, a secreted matricellular protein, has a role in the pathogenesis of psoriasis, and thus targeting CCN1 may represent a potential new therapeutic strategy in psoriasis treatment.

In addition, a positive feedback loop between CCN1 and the cytokine network may also contribute to the sustained elevation of CCN1 in psoriatic skin. CCN1 not only promotes the production of cytokines (Qin *et al.*, 2014), it is also induced by cytokines, growth factors, and environmental stressors (Chen and Lau, 2009), suggesting that a positive feedback loop may contribute to sustained elevation of CCN1 found in psoriatic skin. Therefore, targeting CCN1 could be an effective therapeutic strategy by inhibiting such a positive feedback loop in psoriasis.

Important role of CCN1 in skin biology

CCN1 could be an important regulator in skin biology, as it impacts both epidermal keratinocytes and dermal fibroblasts. In normal adult human skin, CCN1 is substantially elevated in

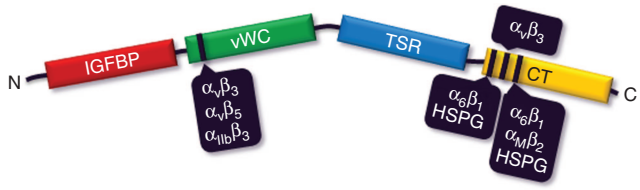

Figure 1. Full-length CCN1 contains 381 amino acids with an *N*-terminal signal peptide followed by four structurally distinct domains (Lau, 2011; Perbal, 2004): an insulin-like growth factor binding protein (IGFBP) domain, a von Willebrand type C repeats (vWC) domain, a thrombospondin type 1 repeat (TSR) domain, and a *C*-terminal (CT) cysteine-knot motif domain. CCN family proteins have an unusually high cysteine content (~10% of residues), and the number and spacing of these cysteine residues are fully conserved in CYR61/CCN1, CTGF/CCN2, NOV/CCN3, and WISP1/CCN4, whereas being largely conserved in WISP2/CCN5, which lacks the CT domain, and WISP3/CCN6, which lacks 4 cysteine residues in the vWC domain. CCN1 promotes diverse and sometimes opposing cellular responses, which can be assigned, as least in part, to disparate activities mediated through distinct integrins expressed by different cell types. Accordingly, CCN1 promotes cell proliferation, survival, and angiogenesis by binding to αvβ3 integrin, and it induces apoptosis and senescence through α6β1 integrin and heparan sulfate proteoglycans (HSPGs).

the dermis by aging, as well as under the influence of ultraviolet irradiation (Quan and Fisher, 2014). Elevated expression of CYR61/CCN1 in the dermis leads to reduced collagen production by impairing TGF-β signaling (Quan and Fisher, 2014) and increasing collagen fibril fragmentation through the production of multiple matrix metalloproteinase proteins (MMPs) (Quan and Fisher, 2014). Thus, elevated CCN1 promotes skin thinning and fragility, two prominent features of aged skin, but interestingly this is not seen in long-standing psoriasis suggesting the involvement of other mitigating factors as well.

Abnormal regulation of CCN1 expression has been observed in several skin diseases, including wound healing and fibrosis (Jun and Lau, 2010). Studies in a mouse model have demonstrated that CCN1 exerts anti-fibrotic activity via induction of dermal fibroblast senescence during cutaneous wound healing. Elevated CCN1 may also have a significant impact on the delayed wound healing seen in elderly patients. CO_2 laser ablation, which causes partial thickness wounding, rapidly and markedly induces CCN1 in human skin dermis *in vivo* (Quan and Fisher, 2014). Timing of the elevated CCN1 levels corresponds to the inflammatory phase (ECM breakdown), and the timing of CYR61/CCN1 diminution corresponds to the ECM remodeling phase (collagen production) of wound healing responses. Also of note, CCN1-regulated factors such as proinflammatory cytokine (IL-1β), collagen-degrading MMPs (MMP-1, MMP-3, and MMP-9), and type I procollagen are well-known components of the wound healing response. These data suggest that CCN1 may have a critical role in regulating wound repair in human skin. Further support comes from mouse studies, which have reported that CCN1 is induced by cutaneous wounding and that it participates in both the inflammatory and remodeling phases of repair (Jun and Lau, 2010). Therefore, the constitutive elevation of CCN1 in aged human skin may delay wound healing by extending the inflammatory phase and delaying the remodeling phase. These findings highlight CCN1 as a possible therapeutic target, not only for psoriasis but also for improving wound healing in the elderly and in skin cancer.

Concluding remarks

The results reported by Sun *et al.* (2015) in this issue reveal the potential role of CCN1 in the pathogenesis of psoriasis. This study, together with other emerging data, suggests that CCN1 may function as an important regulator in skin biology, by modulating key functions of keratinocytes and fibroblasts. Clearly, there remains much to be learned about the regulation of CCN1 and its functions in skin physiology and pathology. It should be noted that CCN1 is one of the six members of the CCN family. CCN2 is a well-established mediator of fibrosis. However, little is known regarding the roles of CCN3-6 in skin biology. Certainly the article by Sun *et al.* (2015) should spur new appreciation of the importance of the CCN family of proteins in skin biology.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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